REMARKS

Claims 2, 4, 5, 7, 9, 11-20, 24, 26, 28-33, 37, 39, 42-68, 70, and 73-79 were pending at the time of the Office Action. Claims 46-61 stand withdrawn. Claims 2 and 4 stand rejected under 35 U.S.C. § 102(b). All claims stand rejected under 35 U.S.C. § 103(a). Claim 39 stands objected to under 37 C.F.R. § 1.75. Claims 2, 4, 16-19, 65, 66, 68, and 69 stand rejected for obviousness-type double patenting. Applicants address each of these rejections and objections below.

Claim Amendments

Claim 39 has been cancelled. New claim 80 has been added. Claim 80 is identical to pending claim 2, except that it does not include Env in the list of proteins. No new matter has been added.

Rejection Under 35 U.S.C. § 102(b)

Claims 2 and 4 were rejected as anticipated by Yu et al. and as evidenced by MESH database 1990. This rejection is respectfully traversed. Yu et al. describe a vector containing the coding sequence for gp120. Claim 2 does not list gp120 as one of the viral proteins to be included in the vector. The closest protein in the list of proteins of claim 2 is Env. Env, as known to those of ordinary skill in the art, is a complex that includes both gp120 and gp41 polypeptides. Thus, Env, recited in claim 2, includes Yu et al.'s gp120,

but also includes gp41. Because Yu et al. do not disclose or suggest the insertion into a Sendai viral vector of a gene encoding the complete Env complex, Yu et al. cannot anticipate claim 2 (or claim 4). Applicants also note that new claim 80 does not recite Env. Accordingly, the rejection of claims 2 and 4 under 35 U.S.C. § 102(b) should be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 2, 16-19, 65, 66, and 68 were rejected for obviousness over Yu et al. in view of Carruth et al. (Page 4 of the Office Action states that the rejection is for anticipation under Section 102 (b). It is believed, based on the text that follows the initial sentence, that this was intended as an obviousness rejection, and the following discussion proceeds on that assumption.)

Yu et al. has been discussed above; the reference does not teach the presence in a Sendai virus vector of any of the proteins of generic claim 2. Carruth does not remedy the deficiencies of Yu et al. In fact Carruth, like countless other references, is a testament to the difficulty of successfully developing an HIV vaccine. Of course, Carruth lists known HIV proteins, again like many other references published during the years-long failed efforts of the scientific community. Carruth contains nothing to suggest that a successful vaccine should express any of those proteins in a Sendai virus vector.

Claims 75 and 78 were rejected for obviousness over Yu et al. in view of Carruth

and Brander et al. Yu et al. and Carruth et al. are discussed above. Regarding Brander et al., the reference merely discloses the fact that p17 was known in the art; Brander et al. contains nothing to suggest the use of that knowledge to create a Sendai-based AIDS vaccine. (Again, this rejection was, in the Office Action, initially mischaracterized as an anticipation rejection.)

Claims 2, 4, 16-19, 65, 66, and 68 stand rejected for obviousness over Nagai et al., Yu et al., Hirsch et al., and Henke et al. This rejection was addressed in the previous Reply, which is hereby incorporated by reference.

Claims 5, 7, 20, 28-33, 42-45, 62-64, and 73 were rejected for obviousness over Flanagan et al., Sakai et al., and Hurwitz et al. Flanagan et al. and Hurwitz et al. were addressed in the previous Reply, which is hereby incorporated by reference. Regarding Sakai et al., that reference adds nothing to Yu et al.; like Yu et al., the protein closest to a protein recited in claim 2 is gp120, with no mention of Env. Further, contrary to the Office's statement, this reference does not report successful in vivo results.

Claims 9, 24, 37, 39, and 70 were rejected for obviousness over Flanagan et al., Sakai et al., Hurwitz et al., Hanke et al., and Ourmanov et al. Only the latter reference has not yet been addressed; the statements made previously about the other references are hereby incorporated by reference. Ourmanov's disclosure of the use of multiple antigens in AIDS vaccines is one of many such disclosures, in references disclosing failed attempts at vaccine development. This reference contains nothing to suggest that it should be

combined with other references to make the successful vaccines of the invention.

Claim 26 was rejected for obviousness over Flanagan et al., Sakai et al., Hurwitz et al., Ourmanov et al., Hanke et al., (all of which have been addressed previously; applicants' comments are hereby incorporated by reference) further in view of Persson et al. and Ruprecht et al. The latter two references do not remedy the deficiencies of the other references. The Office states that Persson establishes that it was "known...to modify the S/HIV genome for safety and efficacy concerns." Of course that was true; if the word "hope without reasonable expectation for success" is substituted for "known," the sentence is more accurate. Likewise, Ruprecht disclosed a "strategy," which has not been shown to succeed. Certainly, nothing in these two new references would have given a scientist in this uncertain field a "reasonable expectation of success."

Claims 76 and 79 were rejected for obviousness over Flanagan et al., Sakai et al., Hurwitz et al., and Brander et al. All of these references have been previously addressed; those comments are hereby incorporated by reference. The Office's statement that because, on page 22 of the specification, applicants summarized prior art references disclosing elements of certain claims, "the disclosure was based on the knowledge in the art..." thereby allegedly rendering the invention obvious, is inapposite. Applicants have never asserted that every element of the claimed invention was unknown prior to the invention, nor does the law so require.

Claims 11-13 and 15 were rejected for obviousness over Flanagan et al., Kast et

al., and Yu et al. Applicants' previous comments on Flanagan et al. and Yu et al. are hereby incorporated by reference. Kast et al., as the Office notes, merely discloses an assay, and one that does not even involve HIV. The combination of references does not render the inventions of the subject claims obvious; those claims, it must again be noted, contain many limitations not suggested by Kast et al., combined with the other cited references.

Claim 14 was rejected for obviousness over Flanagan et al., Yu et al., Kast et al., Seth et al., and Boutillon et al. All but Boutillon et al. have been addressed previously; those comments are hereby incorporated by reference. Regarding Boutillon, the reference merely discloses a CTL assay. Of course, such assays were known at the time of the invention. The disclosure of this assay, alone or in combination with the other cited references, does not suggest the invention of claim 14.

Claim 67 was rejected for obviousness over Flanagan et al., Kast et al., Yu et al., and Hanke et al. All of these references have been addressed previously; those comments are hereby incorporated by reference. None of the references, alone or in combination, teach the use of short or multi-epitope antigen constructs in the Sendai vaccines of the invention.

Claims 74 and 77 were rejected for obviousness over Flanagan et al., Kast et al., Yu et al., and Brander et al. All of these references have been addressed previously; those comments are hereby incorporated by reference. The fact that proteins recited in

the claims were known to be involved in HIV infection falls short of rendering the claimed inventions obvious.

Turning to secondary considerations, it was well-known at the time of filing to all scientists in the field that the AIDS pandemic is an enormous world-wide health crisis, and billions of dollars have been invested in an unsuccessful effort to develop an AIDS vaccine.

As evidenced by Appendices A-C and the translations thereof submitted herewith, a vaccine of the invention was successful in suppression of viral replication in primates (monkeys). Given the long history of failure in the AIDS vaccine field, success such as is reported in the Appendices submitted herewith is the very antithesis of reasonably expected; what is reasonably expected in this field is failure, and the success of the invention constitutes compelling evidence of non-obviousness.

In view of the above, the rejection of all claims under 35 U.S.C. § 103(a) should be withdrawn.

Objection Under 37 C.F.R. § 1.75

Claim 39 stands objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of claim 37. Claim 39 has been cancelled, and this objection is therefore rendered moot.

Rejection for Obviousness-Type Double Patenting

Claims 2, 4, 16-19, 65, 66, 68, and 69 stand rejected for obviousness-type double patenting over claims 1 and 9 of Nagai et al. in view of Yu et al., Hirsch et al., and Hanke et al.

Applicants submit that, for the reasons presented above in connection with the rejections under 35 U.S.C. § 103(a), claims 2, 4, 16-19, 65, 66, 68, and 69 are non-obvious over claims 1 and 9 of Nagai. The obviousness-type double patenting rejection should therefore be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a Petition to extend the period for replying to the Office Action for three months, to and including September 8, 2008, as September 7, 2008 falls on a Sunday.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 9/8/2008

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Appendix A

2007年10月9日　日本経済新聞　1面

国産品、初の治験

東大など　海外で10年にも

エイズワクチン

東京大学、バイオベンチャーのディナベック（茨城県つくば市）、国立感染症研究所などは、共同開発したエイズワクチンの臨床試験（治験）を二〇一〇年にも米国など海外で始める。国際的な治験機関「国際エイズワクチン推進構想（IAVI）」の協力を得ることで基本合意した。日本で開発されたエイズワクチンの治験は初。ディナベックが保有する遺伝子組み換え技術を使って病原体の遺伝子の一部を含むワクチンを開発した。鼻の中にスプレーするとエイズウイルスに感染した細胞を攻撃する免疫細胞が増える。ワクチンを手助けすれば、ウイルスに感染しても発症やほかの人への感染を抑制できると期待される。

サルを用いた動物実験では投与で大部は感染してもウイルスが増殖せず、発症しなかった。海外では複数のエイズワクチンが治験中だが、人と同じ感受性のサルで有効性を確認できたケースは珍しいという。

マイクロソフトのビル・ゲイツ会長が設立した財団などの寄付で運営されているIAVIを通じて一〇年にも数十人規模の健康な人を対象に、安全性と初期的な効果を調べる。順調にいけば大規模な治験に移行、一五年ごろ実用化する見通し。

現在、エイズ感染者は世界で約四千万人。複数の薬の服用で不治の病ではなくなってきた。ただ治療費が高く、感染者増を長く止めるにはワクチンが不可欠とされる。

Translation of Appendix A

The Nekkei dated October 9, 2007

AIDS Vaccine. First clinical trials for a Japanese vaccine. University of Tokyo and others. Overseas in 2010

The University of Tokyo, DNAVEC Corporation, a biotech company based in Tsukuba, Ibaraki, and the Japanese National Institute for Infectious Diseases and others will initiate clinical trials of an AIDS vaccine which these members have co-developed. The trials are planned to start in 2010, in the United States and other countries outside of Japan. It has been basically agreed that the International AIDS Vaccine Initiative (IAVI), a global clinical trial organization will collaborate. This will be the first clinical trial for an AIDS vaccine developed in Japan.

A vaccine which includes part of the genes of the pathogen was developed using DNAVEC gene vector technology. Intranasal spraying increase the number of immune cells which attack cells infected by the AIDS virus. Inoculation with this vaccine is hoped to suppress the onset of AIDS and the spread of AIDS, even in people who are infected by the AIDS virus.

In animal trials using monkeys, administration suppressed the proliferation of the virus and the onset in 60% of the monkeys infected with the virus. Several other AIDS vaccines are in clinical trials overseas, however, this is a still rare case in which efficacy has been confirmed in monkeys, which belong to the same class as man, that is, primates.

The IAVI, which operates on donations from foundations, including the foundation established by Bill Gates of Microsoft, will investigate safety and initial effects in healthy humans in 2010. If things proceed smoothly, large scale trials will be conducted and the treatment will be available from 2015. The number of people worldwide infected with AIDS is approximately 40 million. Thanks to cocktail therapy (the use of several drugs in parallel) AIDS is no longer an incurable disease. However, the cost of treatment is high and vaccine therapy is considered as indispensable to suppress the increase in the number of infected patients.

2007年11月5日　日本経済新聞　21面

国産エイズワクチン臨床試験へ

「粘膜に投与」強く期待

東京大学とベンチャー企業、ディナベック（茨城県つくば市）などが開発したエイズワクチンの臨床試験が海外で始まることになった。非営利の国際機関「国際エイズワクチン推進構想」が実施する。同機関の最高経営責任者（CEO）、セス・バークレー博士が来日したのを機に、世界におけるエイズワクチン開発の現状と、日本のワクチンの評価を聞いた。

――世界のワクチン開発の状況は。

現在、約三十種類のワクチン候補が臨床試験中だ。いずれもエイズに感染した細胞を排除し、ウイルスの増殖を抑える。感染を防ぐことはできないが、ほかの人に感染が広がるのを抑え、発病を防ぐ。最終的には感染自体を防ぐワクチンが必要だが、まだ臨床試験の段階には来ていない。

現在試験中のワクチンは似通ったものが多く、一つが失敗するとほかにも影響する。日本のワクチンはほかと似ていない独自のもので、非常に期待している。

IAVI バークレーCEOに聞く

世界30種の中でも独自性

――どのような点で期待しているのか。

サルを使った試験で効果が確認されていることと、鼻の粘膜から吸収できることの二点だ。ウイルスは性交時に粘膜を介して入り込む。粘膜で働くワクチンは、ウイルス増殖を効果的に抑える可能性がある。臨床試験中のワクチンで粘膜に投与できるものはない。

――臨床試験計画の見通しは。

品質検査など経て二〇一〇年にも米国で安全性試験を始める。確認できたら感染率の高い地域で効果を調べる。ケニア、ルワンダ、ウガンダのいずれかになろう。六百―七百人規模の臨床試験で有望との手応えが得られたら即座に大規模試験を世界同時に実施する。最短で二〇一五年ごろに実用化される見通しだ。

――エイズには治療薬もある。

治療薬は有効だが、問題の解決にはならない。現在、一人が新たに治療を受ける間に六人が感染している。主要八カ国（G8）はすべてのエイズ患者に治療薬を提供するとしているが、コストは二〇一五年までに年間五百四十億ドル（六兆二千億円）に達すると国連は指摘している。ワクチンが絶対に必要だ。

――ワクチン開発には悲観論もある。

ワクチンでの感染防御が医学的に可能であることは疑いがない。問題は、安全で効果が長続きし、世界のどこでも使える有用なワクチンをいかに早く開発できるかということだ。（編集委員　吉田忠則）

▼国際エイズワクチン推進構想（IAVI）　エイズワクチン開発のために一九九六年に設立された非営利組織（本部ニューヨーク）。英国に研究所、オランダ、ケニア、南アフリカ、インドに支部がある。ワクチン候補を見つけて投与研究で臨床試験している。これまで十一カ国で六種類の臨床試験を開始した。年間八千四百万ドル（約九十六億円）の予算の大半は、英米、オランダ、スウェーデンなど十カ国・機関の政府助成。米マイクロソフトのビル・ゲイツ会長の財団など民間団体も寄付している。

Translation of Appendix B

The Nikkei dated November 5, 2007

Japanese AIDS vaccine enters clinical trials. Great expectations for "membrane administration". Unique among the 30 vaccines currently being tested. An interview with IAVA CEO, Dr Berkley

Clinical trials of an AIDS vaccine developed by the University of Tokyo and venture company DNAVEC (Tsukuba, Ibaraki) and others will start overseas. The trials will be conducted by an international non-profit organization, the International AIDS Vaccine Initiative. The CEO of this initiative, Dr Seth Berkley, recently visited Japan, and we took the opportunity to interview him and ask about the current state of AIDS vaccine development and how the Japanese vaccine is being viewed.

- How is the current situation regarding the development of vaccines?

"Currently about 30 vaccine candidates are undergoing clinical trials. All of them remove AIDS infected cells and suppress the proliferation of the virus. It is not possible to prevent infection, but, they suppress the spreading of the virus to others, and also prevent the onset of AIDS. Ultimately, a vaccine that will prevent infection itself is required, but at this point in time, such a vaccine has not yet reached the clinical trial stage. Many of the vaccines that are now being tested are similar to each other and if one should fail, this would impact the others as well. We have great expectations for this Japanese vaccine, as it is an original vaccine that is quite different from the other vaccines."

- What sort of expectations do you have for this vaccine?

"Two points are promising, firstly, efficacy has been confirmed in primates, and secondly, that it can be absorbed through the nasal membrane. The virus invades the body through membranes during sexual intercourse. A vaccine that works at the membrane has the possibility of effectively suppressing the proliferation of the virus. Currently, there are no vaccines in clinical trials that can be administered through membranes."

- How is the plan, schedule for the clinical trials?

"After quality inspections and such, safety trials may begin in the U.S. in 2010. If it can be confirmed, we will investigate efficacy in areas with a high level of infection. Probably the area will be chosen from among Kenya, Rwanda, or Uganda. If the vaccine proves itself to be promising in clinical trials with 600-700 subjects, then immediately large scale clinical trials will be conducted worldwide. At the earliest, the vaccine would be ready to be used by 2015."

- There are medicaments for the treatment of AIDS.

"Drugs are effective, but they do not solve the problem. At this very moment, for every one person staring medical treatment, six people are being infected anew. The eight major developed countries (G8) claim that they will provide drug treatment to all AIDS patients, but the UN estimates that the cost to do this will increase to 54 billion dollars per year by 2015. Thus a vaccine is essential."

- Some are pessimistic about developing an AIDS vaccine.

"There is no doubt that it is medically possible to prevent infection by vaccines. The question is how we can develop an effective vaccine that is cheap, has long lasting efficacy, and can be used anywhere in the world, and to develop such a vaccine as quickly as possible."

(Interviewed by Aya Furuta)

International AIDS Vaccine Initiative (IAVI)

A non-profit organization established in 1996 for the development of AIDS vaccines (headquartered in New York). The initiative has a research center in the U.K. and offices in the Netherlands, Kenya, South Africa, and India. The initiative finds vaccine candidates and conducts clinical trials in affiliated hospitals. Up to now, six clinical trials have been initiated in eleven countries. Most of the annual 84 million dollar budget is provided by the governments of ten nations and regions including the U.K., the U.S., the Netherlands, and Sweden. Many private groups, such as Bill Gates' (of Microsoft) foundation also contribute to the Initiative.

Appendix C

HEADLINE NEWS

<< 前の記事　　次の記事 >>

2008年01月25日

【予防エイズワクチン】第I相実施へ-東大医科研グループとIAVI共同で

トラックバック(0)　記事一覧　注目記事　前頁に戻る

関連検索:　エイズ　ワクチン　東京大学医科学研究所

講演する俣野氏

東京大学医科学研究所教授の俣野哲朗氏は、都内で開かれた「ワクチン開発の研究・評価に関するフォーラム」で講演し、予防エイズワクチンの第I相試験を非営利団体「国際エイズワクチン推進構想」(IAVI)と共同で計画していることを明らかにした。俣野氏らは、細胞傷害性Tリンパ球(CTL)誘導能を持つセンダイウイルスベクターを用いた予防エイズワクチンをディナベックと共同開発。サルエイズモデルの実験で免疫不全ウイルスの複製制御効果を得ており、2015年には臨床応用を実現させたい考え。

HIV感染症に対しては、これまで様々な抗ウイルス薬が開発され、HIVの複製がある程度制御できるまでになってきた。しかし、飛躍的な治療薬の進歩にもかかわらず、HIV感染者は世界的に増加し続けているのが現状だ。俣野氏は、感染から発症まで数年かかる慢性感染症を征圧することの難しさを指摘した上で、「HIV感染症の制圧には、グローバルな視点と封じ込めが必要」と述べ、予防ワクチンがHIV感染症克服の切り札との考えを強調した。

HIV感染症の特徴は、慢性持続感染症であるためにウイルスの多様性が生まれ、自然感染の経過で誘導される宿主免疫によって、HIVの

複製が制御されないことにある。そのため、予防エイズワクチンを開発するためには、免疫誘導法の開発に加えて、どのような免疫反応を誘導するかというウイルス複製制御機構の解明が重要になってくる。

こうした中、俣野氏らは、HIV複製抑制に中心的な役割を担うCTLに注目。CTLを効率的に誘導するセンダイウイルスベクターを使った予防エイズワクチンをディナベック社と共同開発した。

この予防エイズワクチンを、サル免疫不全ウイルスを感染させた急性エイズモデルに接種したところ、全てのサルでHIV複製抑制効果が得られたものの、慢性エイズモデルでは、一過性のウイルス量低下が見られるにとどまった。

しかし、一部のサルではHIVの持続感染が阻止されており、サルの慢性エイズモデルで初めて予防エイズワクチンの効果が示された結果となった。

そこで俣野氏らは、部分的なワクチン効果でも、集団としてのHIV感染の拡大阻止効果が期待できると判断し、非営利のIAVIと共同で第I相試験の実施を計画しているところだ。

俣野氏は、「予防ワクチンは製品としての利潤が期待できず、有効性の評価には大規模な臨床試験が必要となるため、非営利組織との連携が必要だ」と強調し、世界的な視野で予防エイズワクチンを開発することの必要性を訴えた。臨床試験の進捗状況によるものの、現段階では15年の臨床応用を予定しているという。

関連記事

- 【肝炎救済】依然として残る難題-傷つく薬害エイズ被害者
  2008年01月18日
- 06年のエイズ発生動向は1358件と過去最高
  2007年05月23日
- エイズ患者・HIV感染者-3年連続で1000人突破
  2007年02月09日
- 【厚労省】中皮腫とエイズ治療薬を緊急収載
  2007年01月19日
- エイズ薬77品目-米国企業が開発中
  2006年12月19日
- 【厚労省】06年度戦略研究は癌とエイズ予防
  2006年05月19日

関連リンク

- 東京大学医科学研究所
- 国際エイズワクチン推進構想（IAVI）

Translation of Appendix C

Yakujinippo Mail News dated January 25, 2008

[Prophylactic AIDS vaccine] University of Tokyo Institute of Medical Science group and IAVI jointly to conduct phase I clinical trials.

Professor Tetsuro Matano of the Institute of Medical Science, University of Tokyo, lectured at the "Forum for the Research and Evaluation of AIDS Vaccine Development" in Tokyo, and revealed that he is planning, in collaboration with the non-profit organization, the International AIDS Vaccine Initiative (IAVI), phase I trials of a vaccine for the prevention of AIDS. Professor Matano and others have, in collaboration with DNAVEC, co-developed a prophylactic AIDS vaccine using a Sendai virus vector with cytotoxic T lymphocyte inducibility. Suppression of replication of the immunodeficiency virus has been achieved in non-human primate AIDS model experiments, and clinical applications are hoped to be realized in 2015.

Various anti-virus drugs have been developed for HIV infection, and it is now possible to control to some extent the replication of HIV. However, despite great leaps forward in pharmaceutical treatments, the number of HIV infected people still continues to increase worldwide. Professor Matano pointed out the difficulties of overcoming chronic infections which take years to proceed from infection to the onset, and stated that "in order to overcome HIV infection, a global viewpoint and containment are required", and emphasized that prophlactic vaccines would be key to overcome HIV infection.

A characteristic of HIV infection is that as it is a chronic long term infection, great diversity emerges within the virus and the replication of the virus is not controlled by the host immunity which is induced during the process of natural infection. Therefore, in order to develop a vaccine for the prevention of AIDS, it is important to reveal the mechanism of virus replication regulation and what kinds of immunoresponses are induced, in addition to developing methods of immune induction.

In this context, professor Matano has focused on the central role played by CTL in HIV replication suppression, and co-developed with DNAVEC a vaccine for the prevention of AIDS using a Sendai virus vector which efficiently induces CTL.

After application of this prophlactic AIDS vaccine to an acute AIDS model infected with simian immunodeficiency virus, the suppression of HIV replication was observed in all monkeys, but in the chronic AIDS model, only temporary reduction of the virus load was observed.

However, in some monkeys, continuous HIV infection was inhibited, and for the first time, the efficacy of a prophylactic AIDS vaccine was indicated in the primate

chronic AIDS model.

Professor Matano judged that even a partial vaccine effect could have potential in suppressing the proliferation of HIV infection and is planning phase I clinical trials together with the non-profit organization IAVI.

Professor Matano emphasized that "as a preventive vaccine cannot be expected to generate commercial gains and large scale clinical trials will be required to evaluate its efficacy, it is necessary to collaborate with a non-profit organization" and furthermore stressed the need to develop a preventive AIDS vaccine from a global viewpoint. Depending on the progress of the clinical trials, clinical applications are at this stage planned for 2015.